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Effects of psilocybin on functional connectivity measured with fNIRS: Insights from a single-subject pilot study

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Abstract

The serotonergic hallucinogen psilocybin has characteristic effects on human brain activity and subjective experience. Previous functional magnetic resonance imaging (fMRI) studies showed alternations of functional connectivity (FC) under the influence of psilocybin in humans. No study, as yet, investigated psilocybin-induced changes in brain hemodynamics and oxygenation with functional near-infrared spectroscopy (fNIRS) optical neuroimaging. Our aim was to perform the first fNIRS single-subject pilot study in order to investigate the ability of fNIRS to detect changes induced by psychedelic substances. To this end, psilocybin (17 mg) was administered orally to a 31-year old man while resting-state changes in cerebral tissue hemodynamic and oxygenation were measured with fNIRS bilaterally over the frontal and occipital cortex. Measurements were performed before the intake of the substance as well as during its effective period (30 min and 60 min after intake). We observed psilocybin-induced changes in the bilateral frontal FC, bilateral occipital FC as well as right and left fronto-occipital FC. In addition, the pulse rate of the subject showed non-random variations during the experiment, possibly related to psilocybin administration. This study demonstrates that fNIRS is able to detect psilocybin-induced changes in resting-state FC. The results of this initial single-subject pilot study are promising and warrants repetition with a larger number of subjects and an improved/extended fNIRS setup. We anticipate that fNIRS neuroimaging will play an important role in future studies investigating the neuronal/physiological effects of psychedelic substances in humans.

Introduction

Psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine) is the active compound in psychedelic mushrooms and its use has recently been decriminalized in two cities in the US (Denver, Colorado, and Oakland, California) [1]. The intake of psilocybin is associated with various neurobiological and psychological acute and long-lasting effects in humans [2] [3] mainly mediated by changes in neurotransmitter systems. The serotonin (5-hydroxytryptamine, 5-HT) system is most affected. Psilocybin stimulates 5-HT, and 5-HT_{2A} receptors in particular [4] [2] [3]. While the binding of psilocybin to 5-HT_{2A} is strongest (IC_{50} = 6 ± 0.5 nM), it also binds to 5-HT_{1A} receptors (IC_{50} = 190 ± 40 nM) and to a much lesser extent to 5-HT_{2B} (IC_{50} = 410 ± 50) [5]. Blocking 5-HT_{2A} receptors with the 5-HT_{2A} antagonist ketanserin before administrating psilocybin therefore causes a dose-dependent reduction of the neurological and psychological effects normally induced by psilocybin, highlighting the importance of the 5-HT_{2A} agonistic effect of psilocybin [6] [7]. Besides effects on the 5-HT system, psilocybin also affects the dopamine (D_2) system as evidenced by a striatal dopamine release [8] and a partial reduction of the psychological effects of psilocybin after administration of the D_2-antagonist haloperidol [7]. Due to the lack of affinity of psilocybin to dopamine D_2 receptors (K_i = 17,000 nM) [9], this effect is most probably mediated by 5-HT receptor activation [8].

Numerous preliminary studies showed positive effects of using psilocybin as an adjunct to treating depression [10], particularly treatment-resistant depression [11], alcohol dependence [12] and tobacco addiction [13] [14]. In the context of psychotherapy, "psilocybin-assisted psychotherapy" [15] [16] has great potential for the treatment of

a variety of psychological problems. The efficacy of this treatment is mediated by personal subjective psychedelic experience [17]. In healthy humans, psilocybin increases positive mood by decreasing amygdala reactivity [18], increases the personality domain of openness (up to 1 year after the administration) [19], and can lead to experiences that "were considered by volunteers to be among the most personally meaningful and spiritually significant of their lives" [20].

Psilocybin-induced changes in brain metabolism as well as tissue perfusion and oxygenation have been seen locally and globally in the brain, accompanied with characteristic changes in functional connectivity (FC) between brain areas (for a review see [21] [22]).The effect of psilocybin on human brain activity has been previously investigated with functional magnetic resonance imaging (fMRI) [23] [24] [11] [25] [18] [26] [27] [28], arterial spin labeling (ASL) magnetic resonance imaging [29], electroencephalography (EEG) [30] [31] [32] [33] [34] [35] [36] [37], positron emission tomography (PET) [38] [39] [8] and magnetoencephalography (MEG) [40], but not yet with optical neuroimaging based on functional near-infrared spectroscopy (fNIRS). fNIRS has the advantage over fMRI of having a higher temporal resolution, delivering information about hemodynamics and cerebral tissue oxygenation independently, and not requires motionless measurements, which reduces the possibility of experimental stress.

Objective

Our objective was to investigate the potential of optical neuroimaging with fNIRS to detect changes in a subject's brain resting-state functional connectivity (RSFC) after intake of psilocybin. The fNIRS technique enables non-invasive measurements of relative changes in hemodynamics and oxygenation (associated with brain activity due to neuro-vascular coupling) by shining light into the head at different wavelengths in the red/near-infrared wavelength region, measuring the diffusively back-reflected light and determining the concentration changes of the oxygenation state of hemoglobin (associated with tissue perfusion and oxygenation) [41]. fNIRS is increasingly used in neuroscientific studies in humans due to its relatively low cost, portability, unique ability to differentiate between tissue hemodynamics and oxygenation with one measurement, and noiseless use that prevents disturbance of the subject during the experiment.

This is the first report evaluating the application of fNIRS to investigate changes in cerebral hemodynamics and oxygenation induced by the intake of a psychedelic substance in general and psilocybin in particular.

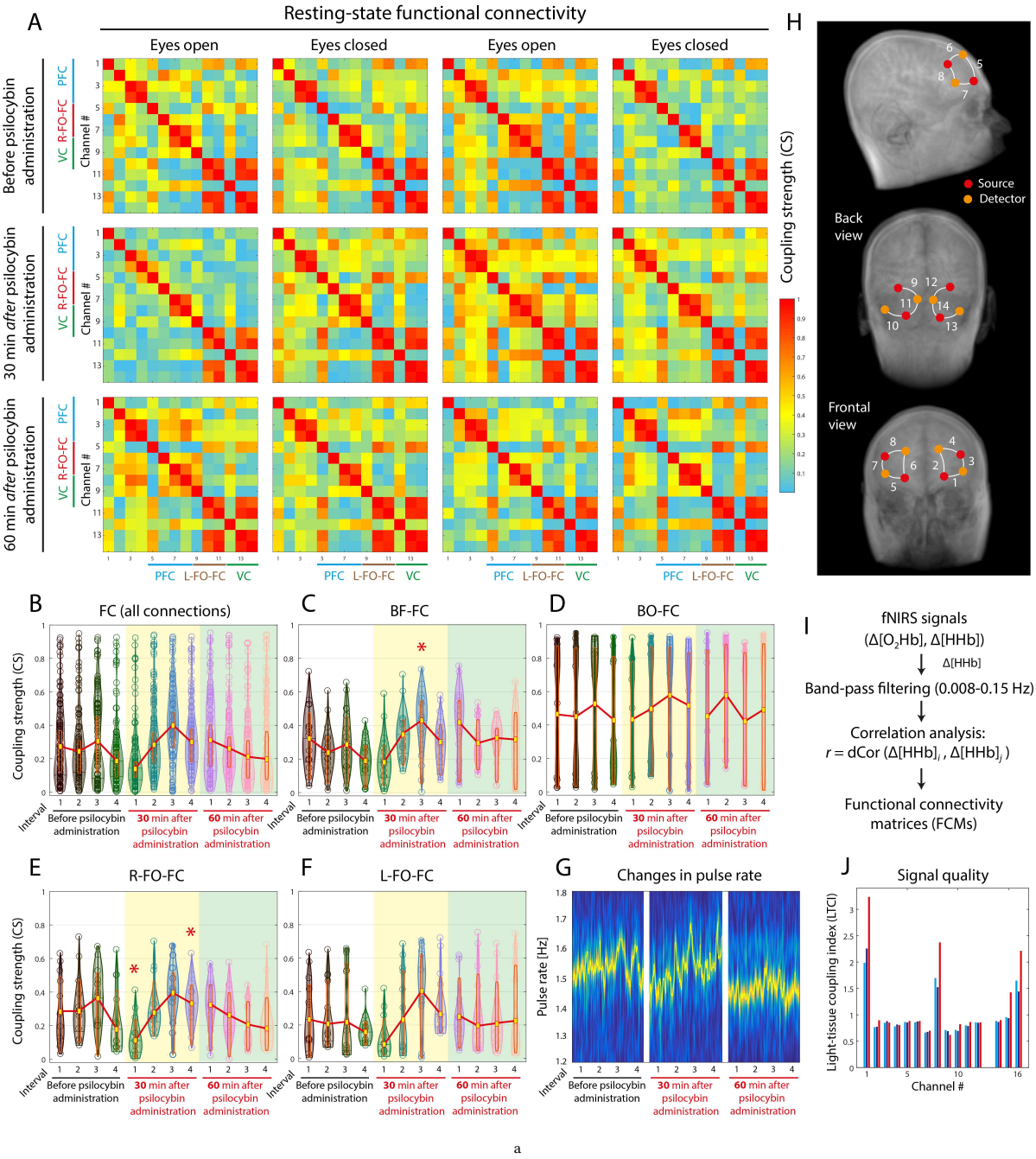

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Figure Legend

Figure 1. Changes in resting-state functional connectivity due to psilocybin administration.

(A) Functional connectivity matrices for the three conditions (before and after psilocybin administration (0 min, 30 min, 60 min) and 4 intervals (of a duration of 3.5 min each; sequence: eyes closed, eyes open, eyes closed, eyes open).

(B–F) Coupling strength values derived from the FCMs for all connections possible **(B)**, bilateral frontal functional connectivity (BF-FC) **(C)**, bilateral occipital functional connectivity (BO-FC) **(D)**, right fronto-occipital functional connectivity (R-FO-FC) **(E)** and left fronto-occipital functional connectivity (L-FO-FC) **(F)**.

(G) Changes in pulse rate during the experiments.

(H) Position of the fNIRS light emitters and detectors on the subject's head. The MRI images correspond to a template implemented in the Brain Viewer software.

(I) Diagram of the key steps of fNIRS signal processing employed.

(J) fNIRS signal quality, as determined by the light-tissue coupling index (LTCI), for the 16 channels used in the study.

VC: visual cortex. PFC: prefrontal cortex. The asterisks indicate statistically significant ($p < 0.05$) differences to the baseline levels (phase 1).

Results & Discussion

The present experimental procedure consisted of 3 phases. Phase 1: baseline, before psilocybin administration, phase 2: 30 min after psilocybin administration, and phase 3: 60 min after psilocybin administration (Fig. 1A–F). Changes in FC during each phase were investigated by dividing each phase into 4 intervals (with a duration of 3.5 min each) during which the subject was asked to close and open his eyes, respectively. We observed changes in bilateral frontal FC (BF-FC) as well as right and left fronto-occipital FC (R-FO-FC, L-FO-FC) with respect to phases 1–3 of the experiment. In particular, during phase 2 the coupling strength (CS) in BF-FC, R-FO-FC, and L-FO-FC showed changes with respect to phase 1 (baseline) (Fig. 1C, E, F). BF-FC showed a statistically significant ($p = 0.0181$) increase compared to baseline (phase 1) at interval 3 in phase 2 (Fig. 1C). R-FO-FC and L-FO-FC first decreased significantly below baseline ($p = 0.0393$ and $p = 0.0072$, respectively) before increasing above baseline with the increase in R-FO-FC in interval 4 being statistically significant ($p = 0.0449$) (Fig. 1E). Psilocybin-induced changes in FC thus occurred 30–45 min (phase 2) after administration in BF-FC, R-FO-FC, and L-FO-FC. No significant change was detected in bilateral occipital FC (BO-FC) (Fig. 1D), but an increasing tendency when analyzing the global FC (Fig. 1B).

The ANOVA revealed no main effects of condition (before drug administration, 30 min afterward and 60 min afterwards) nor time (4-time intervals) for all FC types investigated, but a significant interaction effect between time and condition for the CS values linked to the BF-FC ($F = 2.663$, $p = 0.017$) and L-FO-FC ($F = 2.479$, $p = 0.026$). This highlights the relatively fast changes in RSFC dynamics induced by psilocybin.

Pulse rate (PR) significantly dropped during the experiment ($p < 0.01$) in phase 3 compared to phase 1 (1.452 ± 0.033 Hz vs. 1.534 ± 0.046 Hz, $d = 2.041$) and phase 2 (1.452 ± 0.033 Hz vs. 1.530 ± 0.068 Hz, $d = 1.431$). During phase 2, PR increased and decreased intermittently (Fig. 1G).

We noticed that the recorded fNIRS signals had a different signal-to-noise ratio (SNR) values, quantified by the light-tissue coupling index (LTCI). Only 3 of the 16 channels (18.75 %) had a LTCI value associated with a SNR that would enable reliable detection of small changes in cerebral hemodynamics and oxygenation. Based on this finding, it has to be concluded that our inability to detect strong changes in FC elicited by the psilocybin administration is more likely to be caused by an insufficient SNR of the fNIRS data instead of the absence of a change in FC. The 13 channels without optimal LTCI could still be used in the present analysis since the signals were properly filtered and the signals contained valuable information in the low-frequency domain, which was used in the FC analysis.

Our observation that the most pronounced changes in FC occurred in phase 2 (30–45 min after administration) suggests that this time-frame may also include the strongest neurophysiological effects. Previous studies (involving psilocybin with doses of 10 and 25 mg) concluded that "acute psychedelic effects typically become detectable 30–60 min after dosing, peak 2–3 h after dosing, and subside to negligible levels at least 6 h after dosing" [42]. Our fNIRS FC measures thus responded most likely to the initial phase of the psilocybin effect.

Functional brain connectivity patterns during the resting-state can be separated into the default mode network (DMN), executive control network (ECN), salience network,

dorsal attention network (DAN), auditory network, sensorimotor network and the visual network (VN) [43]. The observation of our study that the R-FO-FC and L-FO-FC showed a change with respect to baseline can be interpreted as a change in the coupling of the ECN or DAN (covering the frontal cortex) with the VN (covering the occipital cortex).

How do our results compare to PET, ASL and fMRI RSFC findings reported in previous psilocybin studies? A direct comparison is difficult since (i) we used a new technique that has its own sensitivity and specificity with respect to changes in hemodynamics and oxygenation associated with brain activity, and since (ii) available RSFC investigations based on fMRI applied different experimental designs than the one used in our study; for example, previous RSFC fMRI studies administered psilocybin intravenously (i.v.) [23] [24] [44] [45] [46] [47], whereas oral administration was used in our case. An i.v. administration of psilocybin causes a fast onset of psychological symptoms and neurophysiological alternations, peaking after approx. 4 min with a steady decline in the following 20 min (i.v. administration of 2 mg psilocybin) [48]. In the first study reported on psilocybin, Carhart-Harris et al. used fMRI and ASL to investigate regional changes of cerebral blood flow (CBF) and FC [23]. A decrease in the blood-oxygen-level-dependent (BOLD) signal and in CBF was found in regions such as the medial prefrontal cortex (mPFC), a central part of the DMN, associated with a decrease in FC between the mPFC and the posterior cingulate cortex. A change in FO-FC as observed in our study has not been reported in this study. Several other publications re-analyzed the study of Carhart-Harris et al. with respect to additional enquiries. These studies found a psilocybin-induced increased FC between the DMN and the right frontoparietal network, auditory network and salience network [44], changes in the complexity of FC [46] [47], increase in BOLD signal variance in the bilateral hippocampi and anterior cingulate cortex [49] [47], and a general increase in the coupling between some of the resting-state networks (with a decrease in coupling in only a few) [28]. Our observation of a change in the right and left FO-FC was also detected in the study by Roseman et al. [28] who noticed an increase in the coupling between the VN and the DAN which covers parts of the region measured in the frontal cortex in the present study. Our observation of a change in the coupling between the right and left PFC has not been reported so far, to the best of our knowledge.

Other physiological responses to psilocybin have been reported such as an increase in the heart rate (HR), in parallel with an increase in body temperature, respiration rate, and blood pressure [50]. Transient increases in heart rate and blood pressure (~15 bpm and systolic blood pressure (SBP) increases of ~20 mm Hg) have been found as acute effects of i.v. psilocybin administration [48]. However, no significant changes in heart rate or blood pressure have been previously reported after the intake of 10 or 25 mg of oral administration psilocybin [42]. Our finding of an increased HR during phase 2 (30–45 min after administration) and a decreased HR (with respect to baseline) during phase 3 (60–75 min after administration) is thus partially in agreement with these findings. A direct comparison, however, cannot be made, since the studies investigating HR changes after psilocybin intake did not report the exact time point of HR assessment. It might be also the case that the HR decrease in phase 3 was caused by increases in tiredness and relaxation of the subject.

The changes in PR suggest a possible change in vascular tone in the cerebral as well as extracerebral tissue due to changes in the autonomic nervous system activity linked to changes in cardiorespiratory activity. Indeed, the vasoactive properties of psilocybin have been reported [51]. While 5-HT receptor-mediated vasoconstriction appears obvious, there are indications that this mechanism is not the only one [51]. If the vasculature was affected by psilocybin during our experiment, the fNIRS signals (as well as BOLD signals recorded with fMRI) would have been affected by this. This aspect should be considered when interpreting the FC fNIRS data and for future fNIRS experiments investigating the physiological effects of psilocybin.

Conclusions

In our single-subject fNIRS study, we detected changes in RSFC during psilocybin ad-

ministration with respect to BF-FC, R-FO-FC and L-FO-FC and associated changes in PR. Our results indicate that fNIRS is able to detect psilocybin-induced changes in RSFC thereby offering a new brain imaging modality to investigate neural and physiological effects induced by psilocybin. Our single-subject study requires repetition within a larger number of subjects and an optimized fNIRS setup (including measurement channels with short source-detector distances, and broader coverage of cortical regions). Measurements with fNIRS have great potential to capture fast dynamical changes of RSFC during psilocybin intake (due to its high time resolution) and are able to capture physiological changes with only minimal disturbance of the subjects as compared to fMRI. We expect that fNIRS will play an important role in future human studies investigating the effects of psychedelics in general.

Limitations

Being a pilot study, the main limitation of our study is that data were collected from only one subject. Nevertheless, our study provides important information on how future fNIRS studies on the effects of psychedelics on cerebral hemodynamics and oxygenation could be improved. Our suggestions are: (i) A good SNR (with a high LTCI for each fNIRS channel) must be ensured for the recorded fNIRS signal. This can be realized for example by optimizing the positioning of the light detectors and sensors on the subject's head. (ii) A larger number of channels is advantageous. Such high-density FC fNIRS measurements (with up to 1200 source-detector channels) have been already demonstrated [52] [53]. (iii) In the present study, only long source-detector channels with a source-detector distance (SDS) of about 3 cm have been used. Having additional channels with short SDS would enable the assessment of changes in hemodynamics and oxygenation originating from extracerebral tissue. Such extracerebral changes can impede the signal originating from deeper layers (cerebral) and can lead to misinterpretation of the fNIRS signal [54] [41] [55]. Adding channels with a short SDS is therefore recommended for future fNIRS studies. Methods are available to regress out extracerebral influences (e.g. [56] [57] [58]). (iv) Changes in respiration and autonomic nervous system can modulate both hemodynamics in the cerebral and extracerebral compartment which could also negatively influence the fNIRS measurements [54] [59] [60] [61] [41] [55]. The removal of these systemic hemodynamic fluctuations is important for fMRI as well as fNIRS. While fMRI provides the availability of standardized methods to remove systemic influences [62] [63], methods addressing this type of confounding factors are still under development for fNIRS [64] [49]. As in the case of the BOLD signal [63], fNIRS signals are not a direct measure of neural activity but reflect a complex combination of changes in metabolism ($CMRO_2$), blood flow and blood volume. (v) A continuous measurement over the whole time course (e.g. 2–3 h) could be advantageous to detect changes in RSFC induced by psychedelic substances in order to optimally capture the dynamics of FC. In the present study, phases 1, 2 and 3 were 15 min apart, resulting in a discontinuous measurement.

Alternative Explanations

Additional Information

Methods

Subject and experimental protocol

A 31-year old male participated in the study and gave written consent. The study was approved by the ethics committee of the Canton Zurich (KEK-ZH-Nr: 2013-0434) and conducted in accordance with the Declaration of Helsinki. Data, in anonymous format (according to data protection policy in the ethics agreement), are available on request.

3 fNIRS measurements were conducted in a male subject before and after (30 min and 60

min) psilocybin administration. Each measurement lasted about 15 min. The first measurement was conducted at 9:15 am, the second one at 10:20 am, and the third one at 11:00 am. The 3 single measurements constituted 3 phases of the measurement (baseline resting-state, 30 min, and 60 min after administration). An oral dose of 17 mg psilocybin was administrated to the participant. During each measurement, the participant was asked to rest quietly in a chair and verbal instructions were given during the measurement to open or close both eyes. During each 15 min measurement, the subject had to repeatedly close and open his eyes each for a duration of 3.5 min. Each of the 3.5 min intervals was used separately for the FC analysis.

Functional near-infrared spectroscopy instrumentation

RSFC measurement was performed with a NIRSport instrument (NIRX Medizintechnik, Berlin, Germany) consisting of 8 light detectors (silicon photodiodes) and 8 light emitters (dual-wavelength light-emitting diodes with 760 nm and 850 nm) at a sampling rate of 7.81 Hz. The light sources and detectors were placed on the head of the subject with help of a specific cap and were positioned over the bilateral prefrontal cortex as well as the occipital cortex (see Fig. 1H). The exact positioning of the sources and detectors was performed according to the 10–20 system. The source-detector separation was about 3 cm. The data acquisition board was connected to a notebook computer running LabVIEW 2011 (National Instruments, Austin, TX, USA).

Functional connectivity analysis

The recorded optical data were converted into relative (to the first measurement timepoint) concentrations of oxyhemoglobin ($\Delta[O_2Hb]$) and deoxyhemoglobin ($\Delta[HHb]$), here referred to as fNIRS signals, with the use of the modified Beer-Lambert law (absorption coefficients (μ_a) for O_2Hb: μ_a (760 nm) = 1486, μ_a (850 nm) = 2526, for HHb: μ_a (760 nm) = 3843, μ_a (850 nm) = 1798; differential pathlength factor (DPF): DPF (760 nm) = 7.25, DPF (850 nm) = 6.38).

The fNIRS signals were band-pass filtered (0.008–0.15 Hz, finite-impulse response filter, zero-phase filtering, filter order: 2000) in order to extract spontaneous fluctuations of oxygenation and hemodynamics and downsampled to a sampling rate of 1 Hz. The frequency range 0.008–0.15 Hz was chosen according to the findings of Braun et al. [65] reporting this frequency band as the most reliable for resting-state connectivity, and the high filter order was chosen according to recent findings of optimal fNIRS signal processing [66].

The quality of the recorded signals, with respect to the SNR, was first inspected visually for each channel and secondly quantified by calculating the LTCI using $\Delta[O_2Hb]$ according to LTCI = HRP/HFNP, with HRP being the heart rate power (sum of the absolute value of the filtered signal in the frequency range 0.5–2 Hz) and HFNP being the high-frequency noise power (sum of the absolute value of the signal filtered with a high-pass filter at a cutoff frequency of 2 Hz). The LTCI corresponds to the magnitude of the blood volume pulsation present in the fNIRS signals with respect to the high-frequency noise primarily caused by improper light-tissue coupling. The LTCI thus representing the SNR. Figure 1J depicts the LTCI values for all channels. Channel 13 had to be discarded from further analysis due to a technical problem. 3 of the channels exhibited a high LTCI value compared to the others, indicating a good SNR. For the analysis, all 15 available fNIRS channels were used despite the differences in LTCI and thus SNR values between the channels. The rationale for doing this was our experience from previous fNIRS studies that channels with a lower SNR still contain low-frequency fluctuations and thus information relevant for resting-state connectivity analysis.

For each of the 3 phases and 4 intervals of the experiment, a functional connectivity matrix (FCM) was calculated by correlating all available channels with each other, i.e. the FC was evaluated to 12 intervals with a duration of 3.5 min each. For the FC calculations $\Delta[HHb]$ was used since it is less influenced by confounding (non-neuronally related) physiological factors compared to $\Delta[O_2Hb]$ and total hemoglobin $\Delta[tHb]$ [55]. The correlation was determined by calculating the distance correlation (dCor) between pairs of signals. With the use of dCor we also captured non-linear correlations and accessed

the degree of dependence between two signals in a robust way [67] [68]. The overall coupling strength, CS, was determined for the following regions of interest (ROIs): bilateral frontal cortex (accessing BF-FC), bilateral occipital cortex (accessing BO-FC), right fronto-occipital cortex (accessing R-FO-FC) and left fronto-occipital cortex (accessing L-FO-FC).

Pulse rate extraction from functional near-infrared spectroscopy signals

From the channel with the highest LTCI (i.e. channel 1), the instantaneous PR (an estimate of the HR) was determined by first decomposing the signal in the time-frequency domain with a wavelet transform and then detecting the instantaneous frequency of the main oscillation using the method and code developed by Iatsenko et al. [69]. The ability and validity to extract the PR from fNIRS signals has been previously reported [70] [71] [72] [73] [74].

Statistical analysis

Data were analyzed using JASP (version 0.9.2.2) employing analysis of variance (ANOVA) and calculating the effect size (Cohen's d). Pairwise analysis of variables (two-sided Wilcoxon rank sum test) was done using Matlab (version 2016b). Results were regarded as statistically significant if $p < 0.05$.

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Ethics Statement

The study was approved by the ethics committee of the Canton Zurich (KEK-ZH-Nr: 2013-0434) and conducted in accordance with the Declaration of Helsinki.

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